REMARKS

The present invention relates in part to methods for predicting the likelihood of a subsequent cerebral vasospasm in patients presenting with subarachnoid hemorrhage.

Claims 1-24 are pending herein. Claims 2, 10, and 24 are amended herein in an effort to clarify the subject matter of the claims for the benefit of the Examiner. These amendments do not in any way alter the scope of the amended claims.

Applicants request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

1. Oath/Declaration

A new combined oath and declaration is provided herewith in accordance with the Examiner's comments.

2. Specification

By the foregoing amendments to the specification, Applicants have corrected the trademark usage cited in the Examiner's comments.

3. Sequence Compliance

A sequence listing is provided herewith in accordance with the Examiner's comments.

4. Claim Objections

A. The Examiner objects to the use of "*A* method according to claim *x*" in the various dependent claims, believing that such claims should read "*The* method according to claim *x*". Applicants respectfully submit that the language to which the Examiner objects properly indicates that the claim refers back to, and further limits, claim *x*, in accordance with 37 C.F.R. § 1.75. It is submitted that a proper dependent claim begins with one of two options: "The [method, composition, etc] of claim . . ." or "A [method, composition, etc] according to claim . . ." Applicants note that MPEP 608.01(n) specifically describes the use of the indefinite article, albeit in the context of multiple dependent claims. Applicants submit that the suggested

amendment is not warranted in the present instance, and respectfully decline to amend the claims according to the Examiner's suggestion.

B. The Examiner objects to the use of certain protein names (TRAIL, TWEAK, and KL-6), referring to these as "acronyms." Applicants respectfully disagree that the use of these names raise any question of identity. Contrary to the Examiner's belief, these terms are well known and understood terms in the art. Whatever name is given to any protein is only meaningful because it is understood in the art, just as any name might appear to be meaningless without the knowledge available in the art. Moreover, the Examiner notes that these terms "may have art-recognized meanings," and offers no evidence as to what other meanings might apply to these terms. Nevertheless, Applicants have amended claims 2 and 10 for the benefit of and as requested by the Examiner.

C. Applicants have amended claim 24 herein in accordance with the Examiner's suggestion.

5. 35 U.S.C. §112, Second Paragraph (definiteness)

Applicants respectfully traverse the rejection of claims 1-24 as allegedly failing to satisfy the definiteness standard of 35 U.S.C. §112, first paragraph.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed.Cir.1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed.Cir.1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more").

Moreover, as the Board of Patent Appeals and Interferences recently pointed out, even a "lack of clarity" is insufficient to establish indefiniteness:

> The threshold for indefiniteness is very high: the claim must be "insolubly ambiguous". . . . If one of skill in the art would understand the scope of the claim when read in light of the specification, then the claim complies with § 112(2).

> Claims need not be models of clarity. As long as the meaning is discernible, then even if construction is difficult and the result equivocal, the claim is nevertheless definite. Exxon Research & Eng'g Co., 265 F.3d at 1375, 60 USPQ2d at 1276; All Dental Prodx LLC v. Advantage Dental Prods., Inc., 309 F.3d 774, 779-80, 64 USPQ2d 1945, 1949 (Fed. Cir. 2002) (no indefiniteness despite the lack of clarity).

A. "Subject-derived markers"

The Examiner contends that the phrase "subject-derived markers" is indefinite because "[i]t is not clear if applicant intends to mean the markers are produced (derived) from the subject or merely that the markers are found in the subject sample." Office Action, page 6. Applicants disagree, and note that the Examiner's comments seem to answer the question. The preamble of claim 1 refers to "characterizing a risk of future cerebral vasospasm *in a subject*," and the claim later refers to the markers being measured as being "*subject-derived*." The plain English meaning of "derived" in this intransitive sense is precisely as the Examiner has described -- produced (derived) from.

Because the phrase, in the context of the claim and the specification, is not "insolubly ambiguous," Applicants submit that the claims meet the definiteness standard of 35 U.S.C. §112, second paragraph, and request that the rejection be reconsidered and withdrawn.

B. "Related" markers

The Examiner contends that the phrases "markers related to" and "markers related thereto" are indefinite because "the characteristics needed to determine whether an unknown could be considered to be [related to a marker are] unknown." Office Action, page 6. To the contrary, the specification provides at paragraph [0093] the following definition:

> The term "related marker" as used herein refers to one or more fragments of a particular marker or its biosynthetic parent that may be detected as a surrogate for the marker itself or as independent markers. For example, human BNP is derived by proteolysis of a 108 amino acid precursor molecule, referred to hereinafter as

> BNP1-108. Mature BNP, or "the BNP natriuretic peptide," or "BNP-32" is a 32 amino acid molecule representing amino acids 77-108 of this precursor, which may be referred to as BNP77-108. The remaining residues 1-76 are referred to hereinafter as BNP1-76.

Additional guidance to the skilled artisan is provided in paragraphs [0092]-[0098] using BNP as an exemplary marker. Thus, the specification makes it clear that "the characteristics needed to determine whether an unknown could be considered to be related" are provided by the known amino acid sequence of the various markers and their biosynthetic parents. In view of this explicit definition, Applicants respectfully submit that the phrase does not rise to the level of being insolubly ambiguous. Because 35 U.S.C. § 112, second paragraph demands no more, Applicants request that the rejection be reconsidered and withdrawn.

C. "Temporal"

Applicants have amended claim 24 according to the Examiner's suggestion, rendering the rejection as moot.

6. 35 U.S.C. §112, First Paragraph (written description)

Applicants respectfully traverse the rejection of claims 68-74 as allegedly failing to satisfy the written description standard of 35 U.S.C. §112, first paragraph.

The rejection is premised on the assertion that "neither the specification nor the claims teach how to define or obtain 'markers related to'" the various markers recited in the claims. Office Action, page 7. The Examiner's assertion is repeated throughout the rejection. *See, e.g.*, Office Action, page 8 ("There is no guidance as to what the 'markers related to' and 'markers related thereto' are"; "The skilled artisan cannot envision the detailed structure of the 'markers related to' and 'markers related thereto'").

As noted above in response to the definiteness rejection concerning the same phrases, the Examiner's assertion is without basis. The specification provides a clear definition and extensive

guidance to the artisan in this regard in paragraphs [0092]-[0098].

Moreover, the rejection is further premised on the incorrect assertion that [t]he skilled artisan cannot envision the detailed structure of the 'markers related to' and 'markers related thereto', thus conception is not achieved until reduction to practice has occurred." Office Action, page 8. Imposing a *per se* requirement that related markers (as that term is defined in the specification) must be "reduced to practice" in the specification in order to satisfy the written description requirement is contrary to the established law. In fact, the Court of Appeals for the Federal Circuit has emphasized again that there is no such *per se* rule:

> [I]t is the binding precedent of this court that Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art.... Rather, we explained that: 'The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.'

448 F.3d 1357, 1367-68 (Fed. Cir. 2006) (emphasis in original).

Applicants respectfully submit that the written description rejection is premised on a misunderstanding of the term "related markers," which is defined in the specification, and on an improper *per se* requirement that such related markers must be reduced to practice. In the present case, the specification makes it unambiguous that the "related markers" recited in the claims are characterized by their structural relationship to the claimed parent marker, and these structures are well known in the art. Thus, given the nature and scope of the invention at issue, and the extensive scientific and technologic knowledge already in existence, it necessarily follows that the present specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. Because the written description

requirement demands no more, Applicants request that the rejections be reconsidered and withdrawn.

7. 35 U.S.C. §102

Applicants respectfully traverse the rejection of claims 1-4 and 19-24 as allegedly being unpatentable under 35 U.S.C. § 102(a) over Jackowski, U.S. Patent 6,235,489; and under 35 U.S.C. § 102(b) over Jackowski, WO00/52476 (the PCT publication corresponding to the Jackowski U.S. Patent). Collectively, the cited publications are referred to below as "Jackowski." Applicants submit that no *prima facie* case of anticipation has been established.

The rejection based on Jackowski appears to be the result of a misunderstanding of the claims on the part of the Examiner. The present claims are drawn to characterizing a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage ("SAH"). As is well known in the art, cerebral vasospasm is a delayed event that may follow on the heels of an acute SAH. In 17-40% of patients, a cerebral vasospasm subsequent to SAH causes a delayed neurological deficit and signals a poor clinical outcome. *See*, Charpentier *et al.*, *Stroke* 30: 1402-8, 1999.

The Examiner acknowledges that Jackowski "is silent with respect to the risk of future cerebral vasospasms." But the Examiner incorrectly contends that "this limitation is deemed inherent to the procedures taught by Jackowski because the determination that the patient's markers are indicative of an ischemic event would necessarily rule out vasospasms (or subarrachnoid hemorrhage)." Office Action, page 9. Applicants note that in such a scenario, if the patient's markers *rule out* a subarrachnoid hemorrhage, such a patient is by definition not "suffering from a subarrachnoid hemorrhage," and so the claimed method has not been performed. On the other hand, if the patient's markers *rule in* a subarrachnoid hemorrhage, Jackowski says nothing about characterizing that patient's future risk of cerebral vasospasm, and so again the claimed method has not been performed.

Whether or not Jackowski can "distinguish and/or differentiate between ischemic and

hemorrhagic events" as the Examiner contends (Office Action, page 9), is of no relevance to the presently claimed invention. What is relevant is that Jackowski provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible.

Because the cited patent fails to disclose the claimed invention, no *prima facie* case of anticipation has been established. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

8. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 6-8, 15, 17, and 18 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 or Jackowski, WO00/52476 in view of Yakovlev *et al., J. Neurosci.* 17: 7415-24, 1997. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above with regard to Jackowski, the entire rejection is premised on the Examiner's apparent misunderstanding of the claims. Jackowski provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible. The secondary Yakovlev *et al.* publication does not cure the defects in the teachings of Jackowski, as it too is unrelated to the claimed subject matter. Instead, Yakovlev *et al.* relates to percussion-induced traumatic brain injury. Like Jackowski, Yakovlev *et al.* provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

9. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 5 as allegedly being unpatentable

under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 or Jackowski, WO00/52476 in view of Ronn *et al.*,WO00/18801. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above with regard to Jackowski, the entire rejection is premised on the Examiner's apparent misunderstanding of the claims. Jackowski provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible. The secondary Ronn *et al.* publication does not cure the defects in the teachings of Jackowski, as it too is unrelated to the claimed subject matter. Instead, Ronn *et al.* relates to the use of NCAM as a marker of stroke. Like Jackowski, Ronn *et al.* provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

10. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 9-11 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 or Jackowski, WO00/52476 in view of Greenberg, Drug News and Perspectives 11: 265-70, 1998. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above with regard to Jackowski, the entire rejection is premised on the Examiner's apparent misunderstanding of the claims. Jackowski provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible. The secondary Greenberg publication does not cure the defects in the teachings of Jackowski, as it too is unrelated to the claimed subject matter. Instead, Greenberg relates to the use of VEGF as a marker in cerebral ischemia. Like Jackowski, Greenberg provides no information on how to

characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

11. 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 12-14 and 16 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Jackowski, U.S. Patent 6,235,489 or Jackowski, WO00/52476 in view of Roger *et al., J. Am. Coll. Cardiol.* 34: 155-62, 1999. Applicants submit that no *prima facie* case of obviousness has been established.

As discussed above with regard to Jackowski, the entire rejection is premised on the Examiner's apparent misunderstanding of the claims. Jackowski provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible. The secondary Roger *et al.* publication does not cure the defects in the teachings of Jackowski, as it too is unrelated to the claimed subject matter. Instead, Roger *et al.* relates to the use of BNP as a therapeutic in decompensated congestive heart failure. Like Jackowski, Roger *et al.* provides no information on how to characterize a risk of future cerebral vasospasm in a subject suffering from a subarrachnoid hemorrhage, or even that such a thing could be possible.

Because no *prima facie* case of obviousness has been established, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. .Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 11/01/2006

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